

Remarks/Arguments

Claim 144 has been canceled. Claim 140 has been amended to recite a method of administering epinephrine to a patient. No new matter has been added. Claims 140-143, 146-150, 153 and 156-173 are pending in the application. Reconsideration is respectfully requested.

Priority

The Examiner requests clarification regarding the Applicant's priority claims. Applicants have further amended the paragraph relating to the priority documents to more clearly specify that the present application takes the benefit of the three provisional applications originally specified in that paragraph.

Claim Objections

The Examiner has objected to claims 161 and 162 as depending from a rejected claim. However, the Examiner maintains the rejection of these claims under 35 U.S.C §103 in the Office Action dated March 5, 2008. Therefore, amendment of these claims to include all of the limitations of claim 140 would not render the claims allowable in view of the 103 rejection. Therefore Applicants have not made such amendments.

Claim Rejections-35 U.S.C. §103

The Examiner maintains the rejection of claims 140-144, 153, and 156-160 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al., (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) for the reasons set forth in the Office Action dated August 7, 2007. In response to Applicants' argument filed November 27, 2007 the Examiner makes the; following points: 1) that explicit motivation is not required to show obviousness in keeping with *KSR Intl. Col. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007); 2) that Applicants' prior arguments rely on features not present in the claims; 3) that the hindsight reconstruction is permitted so long as it takes only into account the level of ordinary skill at the time the invention was made and does not include knowledge gleaned only from applicant's disclosure citing *In re McLaughlin*, 443 F.2d 1392 (CCPA

1971); and 4) that Applicants' claims do not require any specific air flow or specify that the person receiving epinephrine is having difficulty breathing. The Examiner also asserts that administration of epinephrine by inhalation is known and that Applicant's data does not demonstrate unexpected results.

A common theme with regard to points 1-4 above is that the Examiner has failed to view the presently claimed invention *as a whole*. In accordance with MPEP 2141.02, "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)". Applicants' are not merely claiming methods of inhaling epinephrine, instead Applicants' are claiming highly efficient inhalation of epinephrine requiring that at least 50 micrograms of epinephrine be administered in a single breath activated step. The claims also require that the epinephrine be in the form of spray-dried particles having specific characteristics (at least 45% of the delivered dose has an FPF of less than 5.6 microns and the particles have a tap density of less than 0.4g/cm³) which facilitate the highly efficient inhalation of at least 50 micrograms of epinephrine in a single breath activated step. However, the Examiner appears to be asserting that simply because epinephrine is known and is suitable for inhalation, the improvements of the present invention are obvious.

While the Supreme Court in *KSR*, cautions that the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents" (*Id.*, at 1741), the Supreme Court maintains that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently known in the prior art". *Id.*, at 1741. The Supreme Court further notes that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". *Id.*, at 1741. Yet, the Examiner's reasoning for combining Tarara with Slutsky fails to view the teachings of these references as a whole even in view of what was commonly known about epinephrine.

The Examiner appears to assume that “fine particle fraction” (FPF) is achieved based only on Slutsky’s assertion that a high dose of nicotine is delivered in a single breath (see the Office Action dated August 7, 2007, pages 5 and 6). The Examiner’s assumption is incorrect. It is well understood in the art that the concept of “metered dose” is not equivalent to FPF. FPF is determined using a suitable multistage impactor or impinger test and is calculated by weighing the powder present on the impactor plates and mathematically determining the percentage of the total dose having the desired FPF. In the absence of data or information with which to calculate the FPF, it is impossible to determine what the FPF is of any delivered drug dose. Slutsky provides no data whatsoever in which the fine particle dose can be determined and provides no discussion of FPF or other information that correlates to delivery efficiency for a single breath. In fact, Slutsky describes at column 12, lines 20-30, that the nicotine may have a tendency to stick to the inner walls of the inhaler and the filter and it is up to the patient to “shake” the inhaler which clearly does not insure highly efficient delivery of the nicotine contained therein in the absence of data proving that highly efficient delivery has been achieved.

While Tarara does contain data, such data has already been reviewed by Applicant in their response dated July 20, 2006 and repeated below.

The Examiner has also provided no evidence that Tarara actually delivers at least 50 micrograms of any drug, including epinephrine, to a patient in a single inhalation. In Example XXI, for example, Tarara states that the BDP powder dose delivered to the relevant stages of the cascade impactor is “77 micrograms per actuation”. See, paragraph 0318 of Tarara. However, in paragraph 0315, Tarara states that there were twenty actuations. Thus if 300 micrograms of spray dried microspheres were loaded into the inhalation device as stated by Tarara in paragraph 0314, it is not possible that the FPD was 77 micrograms per actuation as 77 micrograms per actuation multiplied by 20 actuations would exceed the total number of micrograms of spray-dried powder initially loaded into the inhaler for delivery. Likewise, if 100% of the drug was delivered over 20 actuations, the amount of drug per actuation could not exceed 50 micrograms. Clearly, something is wrong with the data provided in Tarara’s examples on its face. It is impossible to tell from the data presented in Tarara whether at least 50 micrograms of BDP or for that matter, any other drug including epinephrine, was actually delivered in a single, breath-actuated step.

The quoted sentence is not consistent with other passages of the specification. If the inhaler is loaded with 15 mg of product, which “corresponds to a drug loading ... of 25 to 500 µg per dose.” The preferred embodiments possess at least 50% weight active agent. Thus, of a 15 mg product, 7.5 mg is active agent. If one assumes the 500 µg dose, for example, refers to the amount of drug delivered, (irrespective of the number of actuations required to deliver the drug) then the respirable portion of the product must be far less than that required by the claim. The product cannot have a fine particle fraction of at least about 45%. If one assumes the 500 µg to be the amount of active agent in the inhaler of the 15 mg of product, the drug load is only about 3.3%, well below the preferred ranges. The highest drug load taught here is 10% (500 µg of 5 mg), again far below the most preferred ranges. In short, these numbers, like other numbers in the patent application, appear to be arbitrary and cannot be said to provide any meaningful teaching with respect to how one would deliver an effective dose of epinephrine.

Thus, Applicants have shown that the fine particle fraction of the agents exemplified in Tarara are far below 45% even if one assumed in accordance with the teachings in Tarara that a 500 microgram dose of the exemplified agent was delivered *irrespective of the amount of actuations required to deliver the dose*. Thus, contrary the Examiner’s assertion, the Examiner has failed to provide any references which suggests or discloses a means of modifying Tarara and Slutsky that would be expected to achieve the presently claimed fine particle feature. Therefore, when the teachings of Tarara and Slutsky are fairly viewed as a whole, neither Tarara nor Slutsky when taken alone or in combination teach or suggest highly efficient delivery (delivered dose having an FPF of less than 5.6 microns of at least 45% in a single breath) of any drug including epinephrine.

Furthermore, the Examiner asserts that Applicants’ arguments in view of Slutsky rely on features not present in the claims. This is not the case. Applicants’ point is that when taken *as a whole*, Slutsky simply does not provide teachings that the skilled practitioner would turn to in the context of the present invention or use in combination with Tarara to arrive at the presently claimed invention. In accordance with MPEP 2141.02, “[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)”. As discussed in the Response dated November 27, 2007,

Slutsky is concerned with providing nicotine by pulmonary delivery while at the same time avoiding irritation to the throat and upper airways of the patient. The solutions that Slutsky provides with regard to the comfortable delivery of nicotine are not those that would be sought by the skilled practitioner looking to achieve highly efficient delivery of epinephrine. In one embodiment Slutsky discloses *increasing the resistance* of the inhaler to *slow the administration* of nicotine and thereby provide greater comfort to the patient (column 3, lines 59-61). In another embodiment Slutsky discloses an air by-pass means intended to *reduce the concentration* of the medicament in the air which inhaled by the patient to avoid irritation to the patient's throat (column 4, lines 50-57 and column 12, lines 47-63). In another embodiment, Slutsky discloses that one treatment may consist of *multiple inhalations* of a smaller dose over a period of time (column 7, lines 4-14 and column 12, lines 47-63). Slutsky's need to provide a large dose of a specific drug, nicotine, while preventing irritation is not equivalent to providing an effective amount of drug in a highly efficient manner as is presently claimed. When taken as whole Slutsky does not provide teachings that the skilled practitioner would view as providing highly efficient delivery of any drug including epinephrine. The Examiner mentions that epinephrine may be used in the treatment of glaucoma and thus does not require administration in a crisis presumably in support of the fact that Slutsky's teachings do not lead away from the presently claimed invention. However, a skilled person who is seeking highly efficient delivery of epinephrine is not concerned with treating glaucoma but is concerned with delivering epinephrine in those instances which require highly efficient delivery of the drug. Such circumstances are those outlined in the background section of the present application and generally refer to a patient who has urgent need of the epinephrine. Thus, the necessary features of highly efficient delivery *are already present in the claims* and it is clear that neither Slutsky nor Tarara when taken alone or in combination, teach, suggest or disclose these critical features.

With regard to hindsight reconstruction, the Examiner asserts that hindsight reasoning is permissible so long as it only takes into account the knowledge available to the skilled person at the time the invention was made (citing *McLaughlin, supra*). However, the Examiner has not shown that *as a whole*, the combination of Tarara and Slutsky provide any evidence at all with regard to the features necessary to achieve

highly efficient delivery of any drug including epinephrine. The features of highly efficient delivery i.e. the criticality of the combination of fine particle fraction and tap density to deliver a high dose of the epinephrine via the epinephrine-containing particles was not appreciated at the time of the invention and can only be arrived at by using information that was *not available* to the skilled practitioner at the time of the present invention, such as by improper hindsight reconstruction based on the data and information of the present application. To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The Examiner has failed to provide a reference which teaches a means of modifying Tarara and/or Slutsky to achieve fine particle fraction necessary to achieve the highly efficient delivery of epinephrine at the necessary effective dose as is presently claimed. Clearly, the combination of Tarara and Slutsky do not teach or suggest critical features of the present claims.

The Examiner has failed to show that the claims are obvious in view of the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has maintained the rejection of claims 161-162 under 35 U.S.C. §103(a) as being unpatentable over Tarara et al. in view of Slutsky (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above and further in view of the 56th edition (2002) of the Physician's Desk Reference (hereinafter the "PDR") already of record. The Examiner states that administration of epinephrine to treat a condition for which it is indicated is *prima facie* obvious. If this were true, improved methods of delivery would be *per se* unpatentable and this is not the current state of patent law. Applicants are claiming an improved and highly efficient method for administering epinephrine. As discussed above, the combination of Tarara and Slutsky do not make the present invention obvious. The citation of the PDR adds nothing to this combination other than what is known in the art about indications for epinephrine. Claims 161 and 162 are not obvious in view of the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has maintained the rejection of claims 140-143, 146-150, 159-160 and 162 under 35 U.S.C. §103(a) over Foster (U.S. 2003/0215512) in view of Tarara and Slutsky for those reasons discussed in the office actions mailed on April 6, 2006 and August 7, 2007. In response to Applicants' arguments filed November 27, 2007 the Examiner makes the; following points: 1) That none of the claim limitations were ignored by the Examiner, 2) the Examiner's stated motivation that the skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky's inhaler to deliver formulation in the fewest number of administrations; 3) that in making their arguments, Applicants' rely upon limitations not in the claims; and 4) that Slutsky does not teach away from the presently claimed invention as asserted by Applicants.

In response to the Examiner's point 1, Applicants believe that the Examiner has not addressed where in the combination of Foster, Tarara and Slutsky there is a teaching or suggestion of highly efficient delivery wherein the FPF of the delivered dose is 45% in a single breath. The Examiner asserts that Foster lacks a teaching of a tap density of less than 0.4 g/cm^3 which is allegedly cured by the teachings of Tarara. That Examiner also asserts that Foster discloses the presently claimed FPF. The Examiner concludes therefore that simply because both Tarara and Foster disclose compositions that are designed for pulmonary administration of active agents, the skilled person would have been motivated to combine the references with the expectation that the resulting composition would have been deliverable using Slutsky's inhaler. The Examiner has seriously oversimplified the many variables that go into making a particle composition suitable for inhalation and this highlights the Examiner's misunderstanding of the presently claimed invention.

Tarara discloses hollow and/or perforated microstructures of low density (Tarara Paragraphs 0015). Tarara discloses the many advantages that this specific morphology provides to the particle characteristics [paragraphs 0015 and 0019]. Thus it is clear that this particle morphology is essential to achieve the results disclosed in Tarara. On the other hand, the particles of Foster are very dense. The theoretical tap density can be calculated to be about 1. The morphology of the Foster particles are described as spheroidal or "raisin-like" with surface convolutions, not hollow and perforated as are the particles of Tarara. Clearly the morphology of Foster's particle compositions are just as

important to the results obtained therein. Furthermore, Foster does not disclose the presently claimed FPF of the particles as asserted by the Examiner. The data disclosed in Tables 0232 and 0234 of Foster are not generated using a breath activated device. As defined in the application, the term “single, breath-actuated step” means that the particles are dispersed and inhaled in one step wherein the energy for the dispersion is provided solely by the patient. See, page 57, lines 6-24 of the present specification. Foster instead uses particle dispersion device which first aerosolizes the powder (without breath activation) to form a standing cloud of particles which are then delivered to the aerosol chamber (paragraph 0095 of Foster).

Thus, while both Tarara and Foster provide compositions “suitable for inhalation” as asserted by the Examiner, the compositions disclosed in each reference are no more alike than an antibody composition and a small molecule composition that may both be “suitable for injection”. The Examiner has not articulated how one would combine the teachings of Foster and Tarara to provide a composition suitable for inhalation with the Slutsky inhaler. Indeed it would be necessary to forfeit the very important morphological features of one or the other of the Tarara and Foster compositions in order to make such a combination. As set forth in MPEP 2143.01, “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)”.

With regard to the Examiner’s point 2 above, the Examiner’s stated motivation that the skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky’s inhaler to deliver formulation in the fewest number of administrations is a mischaracterization of Slutsky. When taken as a whole Slutsky is clearly not teaching the delivery of a formulation in the fewest number of administrations. Slutsky is faced with the problem of needing to deliver a drug by inhalation which requires a very high dose (nicotine) in a manner that does not irritate the patient. In the passage relied upon by the Examiner in column 4, lines 47-49 wherein it is stated that the invention *may* contain a single dose of medicament which is intended to be inhaled by the patient in a single breath, that sentence is immediately followed by the sentence stating that if the dose required is sufficiently great an air by pass means is provided to reduce the concentration

of the medicament in the air which is inhaled by the patient. See also column 12, lines 47-63 discussing that while a large dose may be inhaled, it *may* not be possible for the patient to inhale such a large dose without discomfort and multiple inhalers or dilute air are required to resolve the problem.

Furthermore, Applicants have not relied on features not present in the claims to show non-obviousness (Examiner's point 3). Applicants have merely pointed out that the circumstances under which a skilled person would be motivated to improve the delivery of epinephrine are those outlined in the background section of the present application and generally refer to a patient who has urgent need of the epinephrine. A skilled practitioner would not likely be motivated to achieve highly efficient delivery of epinephrine to treat a non-life threatening disease such as glaucoma, for example. Thus, the necessary features of highly efficient delivery *are already present in the claims*. Slutsky's inhaler has not been designed to provide highly efficient delivery. Slutsky's inhaler is instead designed to deliver a drug that requires repeated large doses without irritation to the patient at the sacrifice of highly efficient delivery as evidenced by the various embodiments to limit the flow rate or dilute the concentration of drug or the embodiments recommending that the number of inhalations be increased. The skilled practitioner would not then be motivated to consider Slutsky as a reasonable solution in the context of the present invention or for use in combination with Tarara and Foster to arrive at the presently claimed invention.

With regard to the Examiner's Point 4, Applicants have already discussed those portions of Slutsky that teach away from highly efficient delivery of a drug in a single breath-activated step. In accordance with MPEP 2141.02, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)". On the *whole*, Slutsky teaches an inhaler that is designed to deliver a drug that requires repeated large doses (to mimic the frequency and effect of a cigarette) without irritation to the patient at the sacrifice of highly efficient delivery as evidenced by the various embodiments to limit the flow rate or dilute the concentration of drug or the embodiments recommending that the number of inhalations be increased. In one embodiment Slutsky discloses *increasing the*

resistance of the inhaler to *slow the administration* of nicotine and thereby provide greater comfort to the patient (column 3, lines 59-61). In another embodiment Slutsky discloses an air by-pass means intended to *reduce the concentration* of the medicament in the air which inhaled by the patient to avoid irritation to the patient's throat (column 4, lines 50-57 and column 12, lines 47-63). In another embodiment, Slutsky discloses that one treatment may consist of *multiple inhalations* of a smaller dose over a period of time (column 7, lines 4-14 and column 12, lines 47-63). Slutsky does not provide a fair teaching of highly efficient delivery of a very different drug, such as epinephrine, in a single breath-activated step.

Therefore, the combination of Foster in view of Tarara and Slutsky does not make obvious the presently claimed invention for all of the reasons discussed above. Withdrawal of the rejection is respectfully requested.

The Examiner has maintained the rejection of claim 171 under 35 U.S.C. §103(a) as being unpatentable over Tarara, in view of Slutsky as applied to claims 140-144, 153 and 156-160 above, and further in view of Radhakrishnan (U.S. Patent No. 5,049,389) already of record. The Examiner relies on Tarara and Slutsky as above. The Examiner states that the teachings of Radhakrishnan were set forth on page 10 of the office action mailed on April 6, 2006. The Examiner states that Tarara lacks the teaching of compositions releasing active agents in a sustained manner which is cured by the teachings of Radhakrishnan. The Examiner asserts that it would have been obvious to combine Radhakrishnan and Tarara to obtain sustained release compositions wherein the active drug and excipients do not crystallize within the liposome and which do not undergo sedimentation when suspended. The Examiner concludes that one would expect success because both inventors teach particular compositions for inhalation comprising adrenaline. Applicants respectfully disagree.

In Applicants' response dated November 27, 2007 Applicants argued as follows.

Contrary to the Examiner's assertion, neither Radhakrishnan nor Tarara *teach* "particular" compositions for inhalation comprising adrenaline. Without the benefit of hindsight, one would not have been motivated to choose adrenaline from amongst the many active agents listed in both Radhakrishnan and Tarara. Furthermore, the problem that Radhakrishnan

wishes to solve (sedimentation on resuspension) is a problem encountered upon using a liquid-based nebulizer, not a dry powder inhaler. As such, one of ordinary skill in the art would not combine Radhakrishnan with Tarara and Slutsky to arrive at the claimed method which relies upon the use of a dry powder inhaler. In addition, claim 171 is dependent from claim 140 and includes all the features of claim 140. For all the reasons discussed above, claim 140 is not obvious in view of any of the above cited combination of references; therefore the Examiner's reliance on the teachings of the secondary references is rendered moot.

In response to Applicant's arguments, the Examiner states that 1) the arguments seem off point because the instant rejection is based upon a conclusion of obviousness not anticipation and 2) that the prior art need not address the same problem that motivated Applicants' claimed inventive method. The Examiner further asserts that one of ordinary skill in the art would realize that the use of liposomes would provide for sustained release of epinephrine upon inhalation. The Examiner also asserts that the ordinary skilled artisan would be cognizant that the liquids from the Radhakrishnan formulations could be evaporated to obtain powdered liposomes, which would reasonably be expected to exhibit the sustained release properties *in vivo* after inhalation.

With regard to Point 1, it is well established that a broad generic disclosure is often insufficient to establish that a claim is obvious. *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994). Tarara, for example, discloses epinephrine amongst a list of specific possible active agents that numbers over 100. Likewise, Radhakrishnan also discloses that epinephrine amongst a long list of over 100 active agents. Neither reference provides examples relating to epinephrine and neither reference singles out epinephrine as being preferred. Thus in the face of such broad disclosure, neither reference can be fairly viewed as teaching the administration of epinephrine to a patient in need of epinephrine.

With regard to the Examiner's Point 2, while it is not necessary that the prior art have the same motivation as that of the Applicants' for making the present invention, the Examiner must articulate some reasoning for the combination. The Examiner's reasoning for combining Tarara and Radhakrishnan appears to be that since both teach particulate compositions for delivering drugs by inhalation, the skilled practitioner would be motivated to combine Tarara to achieve sustained release discussed in Radhakrishnan. The Examiner dismisses that fact that Radhakrishnan teaches compositions that are

intended to be delivered as aqueous suspensions and that Tarara's particles are delivered as dry powders. The Examiner asserts that the skilled practitioner would simply "know" that Radhakrishnan's particles can be "dried". However, as discussed above, Tarara's compositions are of a particular morphology comprising perforated microstructures of low density that are preferably hollow in order to achieve the advantages Tarara describes therein such as high dispersability. It is unclear from "Radhakrishnan's disclosure what the morphology of the particles in suspension are other than the size of the aerosolized particles *prior to drying*, much less what the morphology of such particles would be if the skilled practitioner were to decide to dry Radhakrishnan's aerosolized droplets. In addition, Radhakrishnan provides no information as to the size or morphology of Radhakrishnan's particles if the skilled practitioner were to dry them. Thus, while both Tarara and Radhakrishnan provide compositions that are suitable for inhalation, the compositions disclosed in each reference are no more alike than an antibody composition and a small molecule composition that may both be suitable for injection. The Examiner has not articulated how one would combine the teachings of Radhakrishnan and Tarara to provide a composition suitable for inhalation with the Slutsky inhaler. Indeed it would be necessary to forfeit the very important morphological features of one or the other of the Tarara and Radhakrishnan compositions in order to make such a combination. As set forth in MPEP 2143.01, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)".

The Examiner has failed to establish that the present claims are *prima facie* obvious over Tarara in view of Slutsky and Radhakrishnan. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has maintained the rejection of Claims 163-170 under 35 U.S.C. §103(a) over Tarara in view of Slutsky as applied to claims 140-144, 153 and 156-160 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.* (1986) **40**(6), 673-678) already of record. The Examiner states that Tarara lacks the express teaching of C_{max} and T_{max} of different administration routes. The Examiner relies upon Warren to

show that inhalation of 30 puffs (i.e., not in a single breath) of adrenaline from a pressurized aerosol (not a breath actuated dry powder inhaler) are indicative of what one would expect upon inhalation of Tarara's formulations. The Examiner asserts that based on Warren's data, one would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that the such administration would result in maximal adrenaline blood serum levels in a shorter period of time when compared administration by injection. In response to Applicants arguments the Examiner asserts that Applicants attacked Warren individually and that nonobviousness can not be shown by attacking Warren individually when a combination of references are recited. However, this is simply incorrect. In Applicants' response filed November 27, 2007 Applicants made the following arguments.

Warren does not suggest or disclose that it would be obvious to administer epinephrine by a breath actuated dry powder inhaler. The inhaler of Warren relies upon the external energy of a propellant to disperse the drug and then a large number of breaths to deliver the drug. In addition, claims 163-170 are dependent from claim 140 and include all the features of claim 140. *For all the reasons discussed above, claim 140 is not obvious in view of any of the above cited combination of references.* Warren, as the *secondary reference*, provides no substantive teachings that a highly efficient dose of epinephrine can be achieved in a single breath actuated administration from a dry powder inhaler. [emphasis added]

Clearly Applicants did not ignore the other references when responding to the combination rejection that included Warren. For the sake of expediency, Applicants simply did not repeat the litany of arguments previously presented in over 10 pages of response with regard to why the combination of Tarara and Slutsky does not render claim 140 obvious. Warren is a reference which merely describes that which is already known in the art with regard to the comparative effectiveness of epinephrine administered by inhalation and epinephrine administered by injection does not cure the defects of the combination of Tarara and Slutsky. Warren does not provide any additional motivation or teachings over the cited references which are alleged by the Examiner to already "teach" administration of epinephrine by inhalation to patients in need thereof. Even if Warren were to give the skilled practitioner the idea of administering epinephrine by inhalation to a patient with the expectation that such administration would be effective in

the absence of such a teaching in Tarara combined with Slutsky, the Examiner still hasn't provided any reasoning or reference that would lead the skilled practitioner to prepare an improved and highly efficient delivery (claimed FPF and dosage in a single breath activated step) using a prior art breath activated inhaler including Slutsky's for all of the reasons discussed previously in this Response. Applicants do not merely claim the administration of epinephrine by inhalation. Applicants' invention when viewed *as a whole* is directed to methods of improved, highly efficient delivery of epinephrine which requires that at least 50 micrograms of epinephrine in particulate form be delivered to the patient and that at least 45% of the delivered particles have an FPF of less than 5.6 microns. None of the references when taken alone or in combination disclose or suggest such highly efficient delivery of epinephrine. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has maintained the rejection of Claims 172 and 173 under 35 U.S.C. §103(a) as being unpatentable over Foster in view of Tarara and Slutsky and further in view of Drug Information Handbook ("DIH"). The Examiner relies on the teachings of Foster, Tarara and Slutsky as above and relies on the teachings of the DIH as set forth in the office action mailed on April 6, 2006. The Examiner states that the use of epinephrine bitartrate would have been apparent to a skilled artisan because it is "one of the most common salts of epinephrine employed in pharmaceutical formulations." The Examiner relies upon Foster to teach adding a glass former, such as tartrate, and an additional excipient such as leucine in the formulation. Regarding the amounts of each ingredient, the Examiner asserts that the teaching in Foster of a range of 0.05% to 99.0% active agent makes obvious the selection of 11 to 21% epinephrine bitartrate and, with respect to the remaining excipients, it is a parameter that is routinely optimized. The Examiner concludes that one of ordinary skill in the art would have had a reasonable expectation of success upon the combination of the cited references because Tarara, Foster and DIH teach compositions wherein the active is epinephrine and bitartrate salt of adrenaline is commonly used in pharmaceutical formulations.

In the previous response, Applicants provided the following arguments.

While both Foster and Tarara mention adrenaline (epinephrine) as part of a long list of actives, the mere fact that both references disclose overlapping lists of active agents for incorporation of particles does not provide the skilled practitioner with an expectation of successfully mixing and matching specific excipients and active agents in specific amounts. Neither reference discloses or suggests the desirability of producing the specific epinephrine formulation of claims 172 and 173 nor has the Examiner provided any evidence that would motivate the skilled practitioner to combine the teachings of Foster and Tarara and Slutsky in order to prepare epinephrine containing particles. The Examiner has merely concluded that because both references mention both “particles” and “adrenaline” that they should be combined. This is improper.

The specific formulations are not reasonably taught by Foster or the primary reference, alone or when combined with Tarara and Slutsky and the DIH. Foster teaches a nearly infinite number of possible combinations of a large number of active agents and a large number of excipients. There is no guidance within Foster’s broad generic disclosure to couple epinephrine bitartrate, leucine and sodium tartrate in the specific amounts claimed.

The preferred active agents of Foster appear to be proteins, polypeptides and other macromolecules. Although small molecule drugs are also described and may be “adrenalin,” specific salts thereof are not disclosed. It is noted that salts of many drugs are described in the same list. Had Foster intended to teach salts of epinephrine, he would have. With respect to the amount of active agent added, the reference’s range of 0.05% to 99.0% by weight of active agent is, essentially meaningless because it spans the entire range of possible amounts. That is, it is difficult to imagine a therapeutically effective product where the amount of active agent is substantially lower than 0.05%. Further, since Foster appears to rely upon the formation of a glassy matrix and since the Examiner has not shown that epinephrine would be expected to be glassy, it is not clear that Foster teaches a 99.0 or 100% epinephrine formulation. In any event, a range of essentially no active agent to essentially all active agents is not a meaningful teaching of any particular amount of drug to add. The preferred range of between 0.2% and 97% is hardly more meaningful. Para. [0054]. Such a range hardly suggests to the person of skill in the art to select the range between 11 and 21%. The only small molecule working examples carried less than 5% drug. See Example 16.

The excipients of Foster span several columns. The Examiner relies upon the teaching of adding a “glass former” to suggest that sodium tartrate can be added. In fact, the reference suggests that any glass former can be used and, where the drug itself forms a glass, can be omitted altogether. Para. [0064]. Sodium tartrate is one of several glass formers that could be used, in addition to peptides, carbohydrates such as mannitol (when used in combination with, for example, glycine) or lactose, citric acid and sodium citrate. Sodium citrate was the structurally closest glass

former actually used. However, it appears that all of the working examples employed large amounts of glass formers, in various combinations. There is no guidance to select between about 7 and 17% of this particular compound. There is no suggestion that this particular combination would be expected to result in a glassy matrix.

Furthermore, the claims require the addition of a large amount of leucine. Leucine is not disclosed as a preferred excipient (or “additive”) and there is no guidance in this reference which would suggest that it would be desirable to select leucine and add it in a large quantity. The amount of any one excipient is also not described in a meaningful way to suggest a preferred amount as the teachings are limited to 3% to 99.8% by weight [Para. [0079]]. In fact, this passage suggests that such “additives” should be added in an amount less than 20% w/w. The claims require the leucine to be added in an amount between about 62 and 82%. The reference simply provides no motivation to add such a substantial amount of leucine.

Turning to the working examples for meaningful guidance, 66.2% mannitol, 13.1% sodium citrate and 0.7% citric acid was used with 20% zinc-insulin in Example 1; 18.2% mannitol, 59.1% sodium citrate, 0.1% citric acid and 2.6% glycine was used with 20% zinc-insulin in Example 2; 10.1% mannitol, 27.1% sodium citrate, 0.2% sodium ion and 2.6% glycine was used with 60% zinc-insulin in Example 3; 18.3% mannitol, 19.0% sodium citrate, 0.2% sodium ion and 2.6% glycine was used with 60% zinc-insulin in Example 4; 77.3% sodium citrate, 0.1% citric acid and 2.6% glycine was used with 20% zinc-insulin in Example 5; and so on. Not one example employs an amino acid at high concentrations; not one example employs either leucine or sodium tartrate; not one example employs epinephrine, much less epinephrine bitartrate. A sugar is present in almost every working example. The vast majority of the working examples formulate a protein or peptide. Albuterol sulfate, the only small molecule exemplified, was formulated with 95% or 98% lactose. There is simply no motivation in this exceedingly broad disclosure of a nearly infinite number of possible combinations to select the specific excipients of the claims, in the specific amounts and combine them with epinephrine.

In response to Applicants argument, the Examiner states that 1) Applicants arguments are unpersuasive because the active and the excipients are well known in the art and the skilled practitioner would have an expectation of success upon combining these ingredients and 2) that Applicants have not shown the criticality of the particular components mixed.. As discussed in *KSR*, the Supreme Court states that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently known in the prior art”. *Id.*, at 1741. The Supreme

Court further notes that “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does”. *Id.*, at 1741. Yet, the Examiner’s reasoning that simply because the actives and the excipients are well known is not a sufficient as to why the skilled practitioner would choose the specific percentages of active and excipients of the claimed formulation, particularly the high percentage of leucine. Indeed Applicants can show the criticality of a high leucine formulation. Copending USSN 10/392,333. Example 12 on page 77 discloses data indicating that formulations comprising an active ingredient in combination with a high percentage of leucine as an excipient provides extended release of the active ingredient. Formulation **D** of Figures 10 and 11 of copending USSN 10/392,333 most closely compares with the presently claimed formula of claims 172 and 173 and exhibits significantly greater broncoprotection through at least 16 hours when compared with the control.

None of the references when taken alone or in combination disclose or suggest an epinephrine formulation comprising the claimed percentages of active and excipients. Withdrawal of the rejection under this section is respectfully requested.

Double Patenting

The Examiner has rejected claim 144 as being a duplicate of claim 140. Applicants have canceled claim 144 to avoid this rejection.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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Dated: **June 5, 2008**